Peer Review File

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Response to comments by Reviewer A

Comment 1: First, the table before and after propensity score matching is not available. In terms of variables for propensity-score matching, other variables such as AFP or PIVKA-II, tumor location (i.e., periportal or subphrenic location), type of previous treatment (curative treatment such as surgery or ablation vs. non-curative treatment), and disease-free interval > 2 years in patients with prior treatment history may be included for matching to balance the two groups appropriately. Anyway, due to the absence of the table, it isn't easy to know how many variables were well balanced between the two treatment modalities. Nonetheless, I think that tumor location seems quite different between the two treatments, making it difficult to compare the two treatments.

Reply 1: Patients' baseline characteristics before and after propensity score matching are shown in Table 1 and Table 2. We added information about tumor markers, tumor location in relation to vessels and the diaphragm and disease-free interval. Tumor markers and disease-free interval were acceptably similar, even without propensity score matching. On the other hand, tumor location was significantly different between the two groups; perivascular and subphrenic tumors were more common in the SBRT group. The difference was too large to be matched. We agree that this was one of the limitations.

Changes in the text:

Table 1 and Table 2 were revised accordingly. We added sentences regarding the tumor location issue in the methods and the limitation section (page 7, line 15–17; page 8, line 18–19; page 9, line 6–7; page 13, line 13–14).

Comment 2: There are some patients with previous treatment histories of HCCs: [SBRT groups: 90.3% (82/31) and RFA groups: 79.0% (49/62)]. These imply that tumor recurrence may be affected by prior treatments other than current SBRT or RFA, leading to incorrect recurrence-free survival or overall survival. To avoid this problem, patients with at least two years of the disease-free interval may be included in this study.

Reply 2: According to the suggestion, we performed additional analysis of the patients with at least 2 years of the disease-free interval. In our study in the real-world situation, disease-free interval was less than 2 years in more than half patients (59.3%). Thus, the numbers of the subjects became small, and no intergroup significant difference was observed in local recurrence, overall survival (page 10, line 21 – page 11, line 1) or ALBI score (page 9, line 20–22; Table 3). We agree that our results cannot be simply applied to treatment-naïve patients. We added sentences regarding this issue in the limitation (page 13, line 16–20).

Changes in the text:

Additional analysis excluding patients with disease-free interval less than 2 years of local recurrence and overall survival (page 10, line 21 – page 11, line 1) and ALBI score (page 9, line 20–22; Table 3) were added. The limitation section was also revised (page 13, line 16–20).

Comment 3: Given that the study period is from 2014 to 2019, the RFA technique may have evolved. I wonder how often switching RFA using multiple electrodes (either tumor puncturing or no-touch) was

performed during the study period. If RFAs were performed with only a single electrode, the local tumor control rate would be lower than current advanced RFA techniques.

Reply 3: In this study, switching RFA was not conducted. It is true that several reports have shown the efficacy of switching RFA, but this procedure is not common in Japan. Notably, the local control rate in our study (9.7%; median follow-up period, 27.1 months) was not inferior to results of previous reports with switching RFA (12.4–20.5% at 36 months) (ref. 33.34). We added sentences regarding this issue in the methods and discussion section.

Changes in the text:

Methods section: Switching RFA with multiple electrodes was not conducted. (page 6, line 17–18)

Limitation section: 6) Details of the RFA protocol differ among institutions or countries. Although we adopted the standard protocol in Japan (32), other procedures such as switching RFA using multiple electrode or CT-guided RFA are common in other countries. Switching RFA may provide better local tumor control than conventional RFA; however, the local recurrence rate in our study was not inferior to the results of previous studies with switching RFA (12.4–20.5% at 36 months) (33, 34). Other studies have also shown that local control and survival outcomes did not differ between ultrasound-guided and CT-guided RFA (35, 36). (page 13, line 24 – page 14, line 7)

Comment 4: Line 99. Exclusion criteria: Consider to delete 3) refusal to join in the study because of retrospective study design.

Reply 4: In this study, we obtained informed consent in an opt-out protocol; in other words, we provided the chance to refuse joining the study for eligible patients.

Changes in the text: None

Comment 5: Figure 3A. Figure legend (local recurrence) does not correspond with the graph (local recurrence-free survival). If figure 3A indicates local recurrence-free survival, the cumulative local recurrence rate between RFA and SBRT should be added in Figure 3.

Reply 5: Figure 3A and S2A indicate local recurrence. We corrected the figures and their legends.

Changes in the text:

Figure Legends: Figure 3. Kaplan–Meier analysis of cumulative incidence of local recurrence (A) and overall survival (B) (Figure Legends). Figure 2A. Comparison of cumulative incidence of local recurrence (A) and overall survival (B) between patients with and without ALBI score increase.

Corresponding figures were accordingly revised.

<u>Response to comments by Reviewer B</u>

Comment 1: There are multiple English language and grammar changes that need to be made and it needs to be proofread closely for this. For example, in the first paragraph it is stated “In the current guidelines” this should be stated something like “According to current guidelines…”. Another example is “the curability of..”. The word curability is not typically used. Another example is “Thanks to modern” . These types of phrases not typically used in the scientific literature.

Reply 1: We corrected some words and phrases pointed. The paper was edited by a professional language

editor (William R Brown, M.D., director of the International Medical Editing Service, LLC, USA). (Acknowledgements)

Changes in the text:

According to current guidelines, … (page 4, line 4). ; the therapeutic efficacy with RFA … (page 4, line 7–8).

Comment 2: The authors state that the diagnosis was made with contrast-enhanced imaging. What does this mean more specifically? OPTN criteria? There needs to be strict criteria used to diagnose the HCC.

Reply 2: We used LI-RADS criteria to diagnose HCCs. We added a detailed description on the diagnosis of HCCs in the methods section and added a related reference.

Changes in the text:

2) diagnosis established by histology or contrast-enhanced imaging, according to the Liver Imaging Reporting and Data System (18). (page 5, line 11–12)

Comment 3: The described RFA procedure is not in line with typical ablation protocols. Ablations can be performed with US guidance when the lesion is very clearly visualized and the operator is certain they are obtaining an adequate margin. However, to routinely perform every HCC ablation with US, hospitalize the patient, and then perform cross-sectional imaging the next day with repeated procedures performed as necessary, is not conventional. Ablation is typically performed with cross-sectional guidance when needed to ensure the margin is covered during the ablation session. The local recurrence rate for RFA is higher than typically seen in most large ablation series at centers with high experience. The tumors treated here are less than <3cm and in fact the average size reported by the authors is much smaller. Therefore, the recurrence rate for RFA should not be this high. I suspected one of the reasons is the unconventional method of RFA ablation as described above.

Reply 3: The preference of RFA procedures differs by countries. We adopted the standard protocol in Japan. Although CT-guided RFA are widely performed in some countries, available evidence showed that there was no significant difference in the local control rate between CT-guided and US-guided RFA. In fact, the local recurrence rate in our study (cumulative incidence of 9.7% during the median follow-up period of 27.1 months) seems comparable to past reports, though direct comparison of local recurrence rates is difficult because it is influenced not only by tumor size, but also by tumor location and tumor aggressiveness. Nonetheless, we added sentences regarding this issue in discussion section.

Changes in the text:

6) Details of the RFA protocol differ among institutions or countries. Although we adopted the standard protocol in Japan (32), other procedures such as switching RFA using multiple electrode or CT-guided RFA are common in other countries. Switching RFA may provide better local tumor control than conventional RFA; however, the local recurrence rate in our study was not inferior to the results of previous studies with switching RFA (12.4–20.5% at 36 months) (33, 34). Other studies have also shown that local control and survival outcomes did not differ between ultrasound-guided and CT-guided RFA (35, 36). (page 13, line 24 – page 14, line 7)

Comment 4: Furthermore, a major limitation here is that the authors are using SBRT and RFA as a salvage

therapy. This is not a true comparison between single solitary HCC that has presented initially and was treated with either modality. Some of these patients have tumors that are recurrences. It is well known in the literature that recurrence after ablation or TACE promotes more aggressive biology and causes intrahepatic metastases and satellite areas of disease. If this type of tumor is being treated margin of 1cm should be the goal with ablation, not 5mm. The margin issue is further compounded by the fact that the ablation is performed with US guidance. This is a major limitation and really makes it impossible to compare these groups. If the authors would like to do a true comparison they need to exclude patients with prior treatment and only compare initial presentation HCC with SBRT vs RFA.

Reply 4: We agree to the comments. However, in the real-world practice, both SBRT and RFA are often performed for recurrent HCCs with previous therapy than for treatment-naïve HCCs. We aimed to clarify the impact of SBRT on liver function, one of important concerns of radiotherapy, and efficacy in the real-world setting. We added sentences regrading this issue in the limitation section. We believe that our study still provides helpful results for common clinical practice. The margin of 5mm was not a definitive goal, and we adjust the ablation area based on tumor location and its aggressiveness. We added sentences regarding these points in the methods section.

Changes in the text:

Limitation section: 4) Most patients in this study had previous been treated for HCCs. When we excluded patients with disease-free intervals of less than 24 months, no significant intergroup difference was observed in local recurrence or the longitudinal change of ALBI scores. Thus, our results cannot be simply applied to patients for treatment-naïve HCCs. (page 13, line 16–20)

Method section: …; the margin setting was modified appropriately based on tumor location and its aggressiveness. (page 6, line 16–17)

Comment 5: The authors make a final conclusion that SBRT may be considered an alternative to RFA for small HCC. This conclusion cannot be drawn from the results of this paper. The first issue is the comparison group as described above, with many patients receiving this as salvage therapy. Secondly, it has been shown in the literature that the pathologic necrosis rates are much higher with ablation then SBRT. Furthermore, SBRT has higher toxicity, as mentioned in this paper, and this becomes an issue when they need additional treatment in the future in the setting of cirrhosis and portal hypertension.

Overall, the underlying comparison groups in this paper are flawed and the ablation technique used does not follow standard protocol. If the authors would like to revise this paper I recommend narrowing down the comparison groups and re-assessing what conclusions can truly be drawn from the new data.

Reply 5: Following the reviewer's advice, we revised the conclusion to focus on the effect of SBRT on liver function rather than the comparison of its efficacy with RFA. As we stated in Reply 4, we believe that our study still provides helpful results for common clinical practice.

Changes in the text:

Abstract: SBRT had modestly negative impact on liver function but with appraisable local control of HCC. Our findings should contribute to the selection of this modality for treatment of single, small HCC. (page 3, line 19–21)

CONCLUIONS: SBRT had modestly negative impact on liver function but with appraisable local control of

HCC in the real-world practice for single, small HCC. These advantage and disadvantage of SBRT should be considered in selecting the treatment modality, and long-term monitoring of liver function is advised after SBRT, especially in patients with pretreatment impaired liver function (page 14, line 9–13).